A Systematic Approach for Post Hoc Subgroup Analyses With Applications in Clinical Case Studies

Christoph Muysers
Bodo Kirsch

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Further co-authors of paper:
The next 20 minutes

// The demand for subgroup analyses

// The ‘Subgroup Explorer’ (tool)

// The ‘Subgroup Screening’ (procedure)
Subgroup Analyses

medically important -- regulatory requirement -- many stakeholders
Even ‘Important’ only Subgroups can be Overwhelming

... factors used in **stratification randomisation** // factors with some **biological plausibility** or **external evidence** where **heterogeneous** response might be hypothesised // at least **demographic factors**, including **genomic factors**, related to the mechanism of action pharmacology // in addition, careful consideration should be given to other **factors that might plausibly be predictive for different response** to treatment **such as stage, severity or phenotype of disease**, use of **concomitant medications** and **possibly region**, country, or centre // truly exploratory analyses should be planned for the **spectrum of demographic, disease and clinical characteristics**, including those factors a particular factor there is good argumentation why homogeneity of response to treatment is plausible // analysis of the **complement subset** should also be displayed // review of **other exploratory analyses** // exploration of interactions and effects in subgroups **on different scales** // analyses of continuous variables using **different cut-offs** should routinely be performed ... *

* EMA 2019, Guideline on the investigation of subgroups in confirmatory clinical trials*
From Forest Plots to In-depth Subgroup Screening

Overall
- Age X Sex
- Age X Race
- Age X Weight [kg]
- Age X BMI [kg/m^2]
- Sex (Male; Female)
- Race (White; Black; Asian; Other)
- Weight [kg] (<60; ≥60 - <90; ≥90 kg)
- BMI [kg/m^2] (<25; ≥25 - <30; ≥30 kg/m^2)
- CrCl [mL/min] (<30; ≥30 - <50; ≥50 - ≤80; >80 mL/min)
- Index Event (STEMI; NSTEMI; Unstable angina; NSTEMI+Unstable Angina)
- Prior MI (yes, no)
- PCI for Index Event (yes, no)
- Elevated Cardiac Biomarker (yes, no)
- Congestive Heart Failure (yes, no)
- Prior Ischemic Stroke/TIA (yes, no)
- Hypertension (yes, no)
- Diabetes (yes, no)
- Region (East Europe; Western Europe; North America; South America; Asia; Others)
- Age X Region
- Age X Index Event
- Age X Prior MI
- Age X PCI for Index Event
- Age X Elevated Cardiac Biomarker
- Age X Congestive Heart Failure
- Age X Prior Ischemic Stroke/TIA
- Age X Hypertension
- Age X Diabetes
- Race X Region
- Race X Index Event
- Race X Prior MI
- Race X PCI for Index Event
- Race X Elevated Cardiac Biomarker
- Race X Congestive Heart Failure
- Race X Prior Ischemic Stroke/TIA
- Race X Hypertension
- Race X Diabetes
- Sex X Region
- Sex X Index Event
- Sex X Prior MI
- Sex X PCI for Index Event
- Sex X Elevated Cardiac Biomarker
- Sex X Congestive Heart Failure
- Sex X Prior Ischemic Stroke/TIA
- Sex X Hypertension
- Sex X Diabetes
- Weight X Region
- Weight X Index Event
- Weight X Prior MI
- Weight X PCI for Index Event
- Weight X Elevated Cardiac Biomarker
- Weight X Congestive Heart Failure
- Weight X Prior Ischemic Stroke/TIA
- Weight X Hypertension
- Weight X Diabetes
- BMI X Region
- BMI X Index Event
- BMI X Prior MI
- BMI X PCI for Index Event
- BMI X Elevated Cardiac Biomarker
- BMI X Congestive Heart Failure
- BMI X Prior Ischemic Stroke/TIA
- BMI X Hypertension
- BMI X Diabetes
- Age X Sex
- Age X Race
- Age X Weight [kg]
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From Forest Plots to In-depth Subgroup Screening
From Forest Plots to In-depth Subgroup Screening
Subgroup Explorer
and the Exploration Hub

https://cran.r-project.org/web/packages/subscreen/
explore factor level combinations

compare subgroups for two endpoints

evolution of all factors at a glance
Feature: Importance Tab
Machine learning based prioritization of analyzed factors

Information about variable importance based on a random forest algorithm

Illustration taken from Random Forest R-package
https://kogalur.github.io/randomForestSRC/theory.html
### Table of Selected Subgroups

<table>
<thead>
<tr>
<th>Memorize</th>
<th>SGID</th>
<th>Number of Subjects</th>
<th>Mean_changeTS_at52</th>
<th>nFactors</th>
<th>PerProtocol</th>
<th>EOGD_score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Memorize</td>
<td>452</td>
<td>270</td>
<td>8.3</td>
<td>2</td>
<td>Y</td>
<td>Worst QOL</td>
</tr>
</tbody>
</table>

**Legend:**
- **Memorize** - Memorize selected row(s).
- **SGID** - Subject Group ID.
- **Number of Subjects** - Number of subjects in the subgroup.
- **Mean_changeTS_at52** - Mean change at 52 weeks.
- **nFactors** - Number of significant factors.
- **PerProtocol** - Indicates per-protocol analysis.
- **EOGD_score** - Expected overall group difference score.
1 to 2 Factorial Subgroups (T239)

Selected Subgroups

Table of Selected Subgroups

- **Memorize**
  - SGID
  - Number.of.Subjects
  - Mean_change1T5_wt2
  - nFactors
  - PerProtocol
  - EGSD_score

<table>
<thead>
<tr>
<th>Memorize</th>
<th>SGID</th>
<th>Number.of.Subjects</th>
<th>Mean_change1T5_wt2</th>
<th>nFactors</th>
<th>PerProtocol</th>
<th>EGSD_score</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
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<td>-1.3</td>
<td>2</td>
<td>N</td>
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<tr>
<td></td>
<td></td>
<td>Best OQL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Biostatistics: Original Research

A Systematic Approach for Post Hoc Subgroup Analyses With Applications in Clinical Case Studies

Christoph Muysers, MSc1@, Alex Dmitrienko, PhD2, Hermann Kulmann, PhD1, Bodo Kirsch, MSc1, Susanne Lippert, MSc1, Thomas Schmelzer, PhD1, Anke Schulz, MSc1, Nicole Mentenich, MSc1, Heinz Schmitz, MD, PhD3, Matthias Schaefers, MD, PhD3, Gerald Meinhardt, MD, PhD4, Thomas Keil, MD, PhD3, and Stephanie Roll, PhD3

Abstract
Background: The analysis of subgroups in clinical trials is essential to assess differences in treatment effects for distinct patient clusters, that is, to detect patients with greater treatment benefit or patients where the treatment seems to be ineffective.

Methods: The software application subscreen (R package) has been developed to analyze the population of clinical trials in minute detail. The aim was to efficiently calculate point estimates (eg, hazard ratios) for multiple subgroups to identify groups that potentially differ from the overall trial result. The approach intentionally avoids inferential statistics such as P values or confidence intervals but intends to encourage discussions enriched with external evidence (eg, from other studies) about the exploratory results, which can be accompanied by further statistical methods in subsequent analyses. The subscreen application was applied to 2 clinical study data sets and used in a simulation study to demonstrate its usefulness. Results: The visualization of numerous combined subgroups illustrates the homogeneity or heterogeneity of potentially all subgroup estimates with the overall result. With this, the application leads to more reported danger of future trials. Conclusion: This described approach supports the
In the past we draw a single conclusion based on a heterogenous study population.
Imagine a tool (such as ‘subscreen’) that allows efficient subgroup analyses for many stakeholders interactively.
Contact

e-mail: Bodo.Kirsch@bayer.com

R-PACKAGE: [https://cran.r-project.org/web/packages/subscreen/index.html](https://cran.r-project.org/web/packages/subscreen/index.html)
Thank you!
at a glance

exemplary data